Comments from Wyeth on the Assessment Report for the appraisal of bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma

Introduction

Wyeth welcomes the opportunity to comment on the Assessment Report (AR) for the appraisal of bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma (RCC), focusing on the technical content relating to the assessment of temsirolimus (Torisel®)

We address concerns over the interpretation of the clinical baseline characteristics and the conclusions drawn from the results of the pivotal phase III clinical trial as set out in the AR.

It would appear that the critique of the model submitted by Wyeth to estimate the cost effectiveness of temsirolimus treatment and its comparison with the PenTAG model is based on a misunderstanding of the data used to populate the Wyeth model and by a lack of clarity of the methods and assumptions used in its development. These issues are addressed in order to provide assurance of the robustness of the model submitted and confidence in the conclusions derived from it.

We identify a number of discrepancies in the inputs to the PenTAG model and in the face validity of some of the estimates of incremental cost effectiveness derived from it. In particular the analyses have been based on a price per 30 mg vial of £618, while the price of temsirolimus provided by Wyeth was £515 per 30mg vial. Thus, the base case result for the ICER is an overestimate and the result of the sensitivity analysis based on £515 reflects the actual **base case ICER of £81,687** (and not £94,385 as stated in the AR).

We believe that some important conclusions of the AR are inaccurate and/or misleading and therefore the report should undergo revision before reaching the Appraisal committee members.

This document contains two parts: comments in free text addressing key issues raised in the AR, followed by a table summarising these and other issues identified by Wyeth and referenced by AR Section and Page Number.

Comments on the Assessment Report

1. Executive Summary (pp. 1 – 12)

On page 1, Sutent is described as ‘novel’ when in fact it is one of two tyrosine kinase inhibitors to be licensed, simultaneously, for the treatment of RCC. It is therefore misleading to apply the term novel to this agent. The novel agent in this assessment is Torisel – the only mTOR inhibitor licensed for the treatment of cancer.

On page 9 the AR states that there is a large degree of uncertainty in the estimates of overall survival (OS). Wyeth would like to clarify that the data for temsirolimus shows a proven OS benefit: this was the primary efficacy endpoint in the phase III trial and the OS benefit for temsirolimus was shown to be statistically, as well as clinically significant, the acceptance of which by the EMEA formed the basis of the approved EU marketing authorisation. The statement as it stands may therefore be misleading.

2. Background (pp. 13 – 34)

Section 2.2 Epidemiology of renal cell carcinoma

Whilst sections 2.1.1, 2.2.1 and 2.2.4 describe the staging, incidence and prognosis of RCC respectively, the number of patients eligible for treatment with temsirolimus, in accordance with its licensed indication, is not acknowledged in the AR. Wyeth estimate that of the 7,000 patients diagnosed with kidney cancer each year in the UK only approximately 450 patients will have advanced RCC with at least 3 of 6 prognostic factors. At less than 1,000 patients this constitutes what NICE refer to as an ultra-orphan condition. The Institute has identified that there may be implications in accessing the cost effectiveness of drugs to treat such conditions and have proposed the need to consider higher cost effectiveness thresholds in line with currently approved ultra-orphan drugs. Thus, whilst estimates of cost effectiveness derived from the Wyeth economic model and the PenTAG economic model are above the threshold range currently applied to conventional appraisals they are below the ICERs that NICE estimates for existing ultra-orphan drugs on the UK market. Given the Citizens Council conclusions and the judgement of the Institute's board that there is public support for the NHS to meet the reasonable treatment costs of expensive treatments for ultra-orphan drugs, the use of temsirolimus to treat poor prognosis aRCC should be considered an appropriate use of NHS resources.

Section 2.7.1.1

P27 It is assumed here that interferon alpha (IFN) may be self administered by patients. Wyeth would like to clarify that according to the SmPC for Roferon-A (the only IFN-α licensed for treatment of RCC):

“Roferon-A should be administered under the supervision of a qualified physician experienced in the management of the respective indication. Appropriate management of the therapy and its complications is possible only when adequate diagnostic and treatment facilities are readily available.”

This comment also applies to Table 40 on page 148.

An informal survey of 15 Oncologists who treat RCC suggests that the percentage of patients (in the 3 of 6 prognostic factor group) unwilling or unable to self administer IFN ranges between centres from 0 – 50%. It may therefore be inappropriate to assume 100% self administration of IFN across all RCC patients.

Section 2.7.4.3

Wyeth would like to correct the Adverse Events listed for temsirolimus. This list, derived from the Hudes study, should read as follows (amendments shown as tracked changes):

"The most commonly reported treatment related adverse events of any grade associated with temsirolimus (experienced by more than 20% of patients) include asthenia, fever, abdominal pain, back pain, ~~bleeding events such as epistaxis,~~ gastrointestinal events including stomatitis, nausea, anorexia, diarrhoea and constipation, ~~cardiovascular events including chest pain,~~ anaemia, hyperlipaemia, peripheral oedema, hyperglycaemia, hypercholesterolemia, dyspnoea and increased infection, cough and rashes."

3. Assessment of clinical effectiveness (pp. 35 – 101)

Section 3.2.1 and 3.2.4.2

Pages 42 and 43 show a table summarizing the quality of information available from the referenced publications of the pivotal trial data for each agent. It is unrealistic to expect that a publication could contain all the information that was assessed here. Whilst Wyeth would have been happy to provide additional information to the Assessment Group during the course of the production of the AR, to enable a more thorough assessment of the quality of the included clinical trial, details of missing information can be found in the full clinical study report which is appended to this document.

Section 3.2.4.1 Population baseline characteristics page 68 and page 138

The AR states that, presumably on the basis that they only have 2 of the original 5 MSKCC risk factors, 25% of patients in the pivotal phase III study are of intermediate rather than poor prognosis. However the definition of poor risk used in the phase III trial and subsequently incorporated into the approved indication on the marketing authorisation for temsirolimus uses an updated version of the MSKCC prognostic model which additionally identifies metastases as a further independent predictor of survival[1]. Poor prognosis in the updated criteria is defined as 3 of the 6 prognostic factors. Given that the overall median OS in the group of patients treated with IFN in the phase III study is only 7.3 months it would be inappropriate to define those patients with 2 original MSKCC prognostic factors and metastatic disease as of intermediate prognosis.

Section 3.2.4.2 page 71

The AR states that the 95% confidence intervals surrounding the estimates of overall survival are 'reasonably wide and approach unity at the upper limit (which would indicate no difference between treatments) highlighting the degree of imprecision of these results. Whilst these comments are made after the results of the final supportive efficacy analyses, utilizing additional follow-up data, and not after the primary efficacy analysis, they do appear to

[1] Mekhail T.M. et al. Validation and Extension of the Memorial Sloan-Kettering Prognostic Factors Model for Survival in Patients with Previously Untreated Metastatic Renal Cell Carcinoma. J. Clin. Oncol. 2005; 23: 832-841

question the validity of the study's findings. The primary efficacy analysis for this study was conducted after 446 deaths had been observed at which point the independent data monitoring committee advised Wyeth that the predefined O'Brien-Fleming boundary for superior efficacy had been crossed, confirming the significantly greater overall survival in patients who received temsirolimus compared with patients treated with IFN. The magnitude of the improvement in OS brought about by treatment with temsirolimus was such that the study was powered to the 2.5% significance level, despite the relatively small sample size. Thus the likelihood of a type 1 error (identifying a significant difference where one does not exist) is low. The trial was continued and as a result of the natural course of disease in these patients, more patients died over time. The patients included in this trial had multiple factors indicating poor prognosis, in the absence of a curative intervention, patients in both active and comparator arms, inevitably die Therefore, as would be expected, at the second analysis point the CI upper limit is closer to unity. However, the CIs do NOT cross unity and that is where the criteria for showing a valid difference is set. It is therefore misleading to suggest that results were imprecise.

Section 3.2.4.2

In Table 23 on page 75, the proportion of patients with clear cell RCC should be 100% for bevacizumab + IFN and 81% for temsirolimus. These figures have been transposed in the table.

Section 3.2.4.2

Page 76 lists the adverse events more commonly associated with temsirolimus treatment compared with IFN treatment but fails to report the adverse events occurring more frequently on IFN treatment. The incidence of fever and chills was higher in patients treated with IFN: 50% of patients on IFN treatment experienced fever versus 24% on temsirolimus treatment, 30% of patients on IFN treatment experienced chills versus 8% on temsirolimus treatment. In addition a higher proportion of IFN treated patients reported vomiting and weight loss than those treated with temsirolimus.

Section 3.2.4.2 Table 25

Error in table: 95% CI for Clear cell should be 0.67 to 1.08.

Section 3.2.4.2 Table 26

Reference should be Dutcher (AR ref. no. 96) rather than Wyeth submission.

Section 3.2.4.2

Table 27, page 80. There are errors in the values quoted in this table – also this data was provided in the Wyeth submission, not the Hudes paper.

The corrected values are highlighted below :

Hazard ratios comparing the temsirolimus and IFN arms were 0.84 (95% CI, 0.63-1.11) and 0.61 (95% CI, 0.41-0.91) for patients with or without prior nephrectomy, respectively.

4. Assessment of cost effectiveness (pp. 102 – 189)

Section 4.4.1.3. Temsirolimus (manufacturer analysis/model)

The critical appraisal checklist of the Wyeth economic model has attracted some unjustified negative comments that we address below. We feel that the model developed is a robust representation of the data from the available phase III RCT.

1. P. 123 Para 2: "An assumption is made that the probability of transition from post-progression to death is equal to that for PFS to death. An assumption is made that the probability of transition from post-progression to post-progression (i.e. remaining in that state) is equal to that for PFS to post-progression. The rationale / support for these assumptions is/are not presented.".

Model assumptions regarding transition from the post-progression state may have been misinterpreted by the PenTAG group in their review. In the Wyeth model, the transition probabilities from the post-progression health state (labelled as Progressive Disease in the PenTAG model) to death are not the same as the transition probabilities from PFS to death. Additionally, the probability of remaining in post-progression is not the same as the probability of transitioning into that health state either.

Wyeth Derivation of Transition Probabilities

The Wyeth and PenTAG models differ in their approaches to using the progression-free and overall survival data: the PenTAG model uses two estimated Weibull functions (one for progression-free survival (PFS) and one for overall survival (OS)), while the Wyeth model uses three Weibull hazard functions (depicted in the influence diagram (See Figure 1)). The three Weibull functions used in the Wyeth model are: 1) PFS to post-progression (*i.e.*, PFS ends as a result of confirmed disease progression, not death); 2) PFS to death (*i.e.*, PFS ends because of death without confirmed disease progression); and 3) post-progression to death (only includes patients who did not die in the PFS state). The specifications used for defining the censored observations for the estimation of each Weibull function are provided in Table 1. To then convert the Weibull functions from survival rate to transition probabilities, we estimated the proportion of people who transitioned out and the proportion who remained at each state. The transition probability was calculated as the proportion of patients who transitioned at time t divided by proportion remained at time t-1. The same method was used to calculate transition probabilities from each of the Weibull curves that were estimated. The probabilities then were implemented in the Markov model to calculate the number of patients at each health state (PFS, post-progression, Death) for each monthly cycle. The advantage of doing the transition probability instead of extracting PFS and OS directly from the data is

that we can trace patients after they have progressed, and have a more accurate estimation of the post-progression costs.

The details of the Weibull function estimation is described below.

Figure 1. Markov state diagram

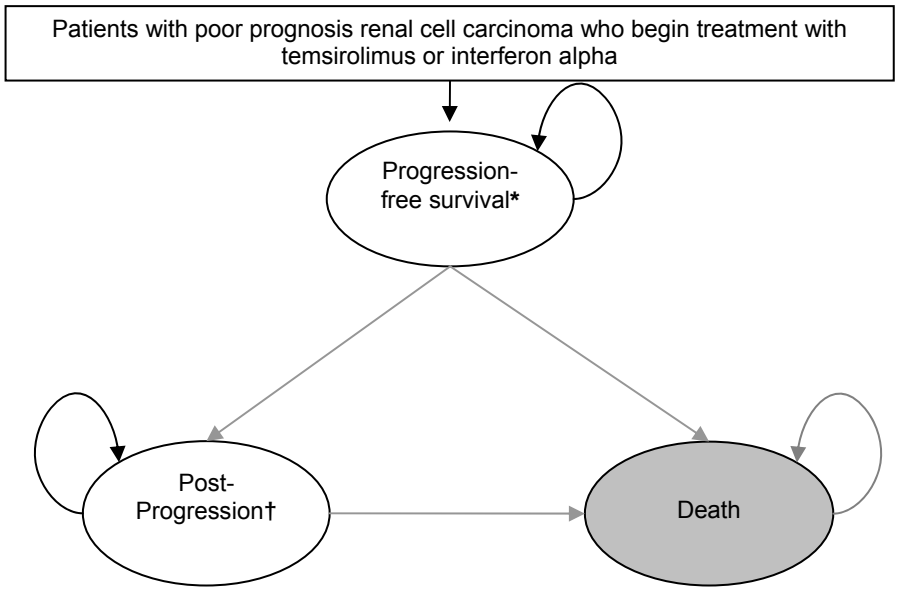


Table 1. Application of transition probabilities

Key:	State:	Possible transitions:	Transition probability:	Notes:
*	Progression-free survival (PFS)**	To Death	Weibull function derived from all patients, using treatment group as an independent variable	patients with disease progression are censored
		To Post-progression		patients who die before progression are censored
		To PFS (remain)	Calculated as remainder	
†	Post-progression	To Death	Weibull function derived from patients with disease progression, treating the date of progression as time zero	Includes patients who receive subsequent treatment and those who receive only BSC
		To Post-progression (remain)	Calculated as remainder	

** Independent Review Committee assessments of progression were used for the base case analysis, sensitivity was tested using the investigator assessment of progression.

2. P. 124 – 125 Review of structure of Wyeth model

After reviewing the PenTAG model and report, we found that the comparisons of model fit presented in PenTAG's Figures 8 and 9 are not accurate. First, the PenTAG model and Wyeth model use different assessments of PFS: The Hudes *et al*. publication Figure 1B presents the Investigator Assessment of PFS, which appears to be the basis of the PenTAG

model, while the base case Wyeth model PFS functions were developed using the independent review committee assessments of progression. The two assessments were made using differing criteria, and thus result in different PFS curves.

Second, and more importantly, the PenTAG model compares two different types of predictions: their predicted PFS/OS based on estimated Weibull parameters, which is used as an input for later model calculations, and Wyeth estimated PFS/OS from the Markov transition simulations, which are part of the model results.

We extracted the overall survival used by PenTAG for life year calculations from their model and present the correct comparisons on predicted OS between the PenTAG model and Wyeth model in the figures below (Figure 2 temsirolimus, Figure 3 IFN). The Wyeth model for temsirolimus has a better fit of the empirical data through the first year and then underestimates survival. The PenTAG model results in a poorer prediction of the first year, but improves thereafter. For the IFN model prediction, neither the Wyeth nor the PenTAG model predict the IFN empirical data as robustly, although from visual inspection, the Wyeth model appears to have has better fit through the first year.

Figure 2. Comparison of overall survival, temsirolimus

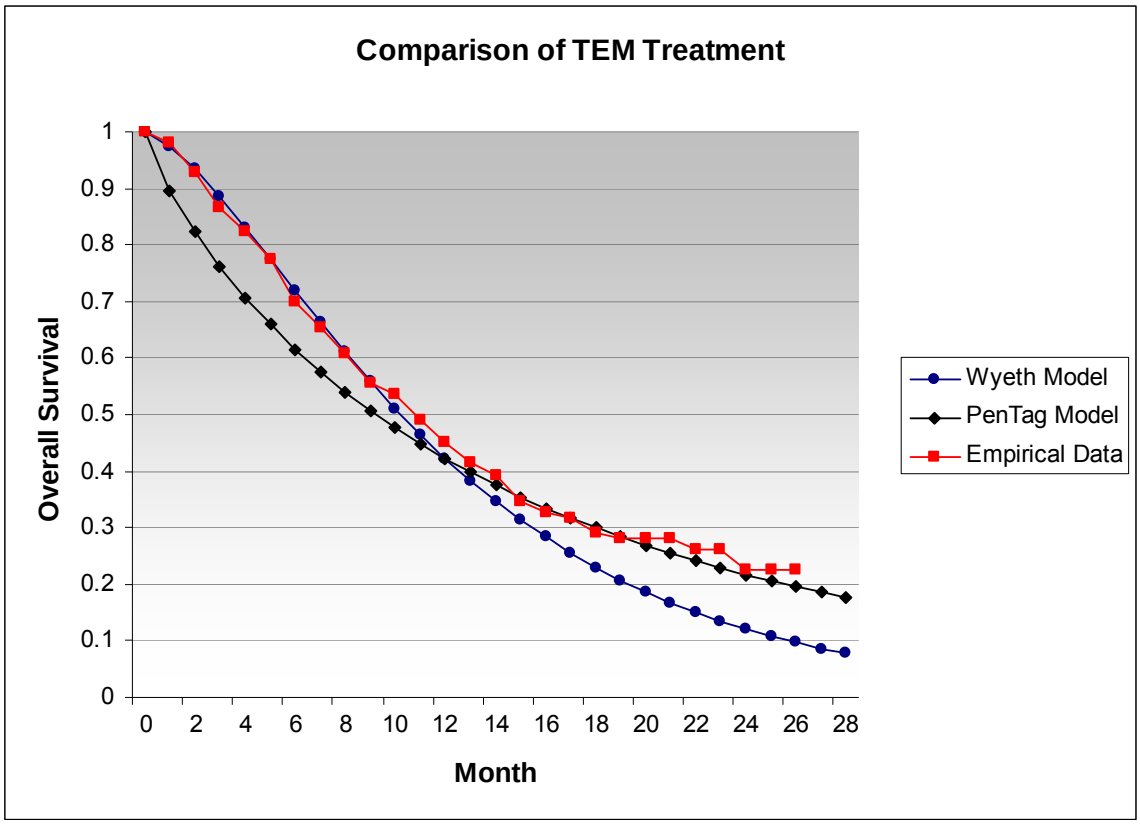
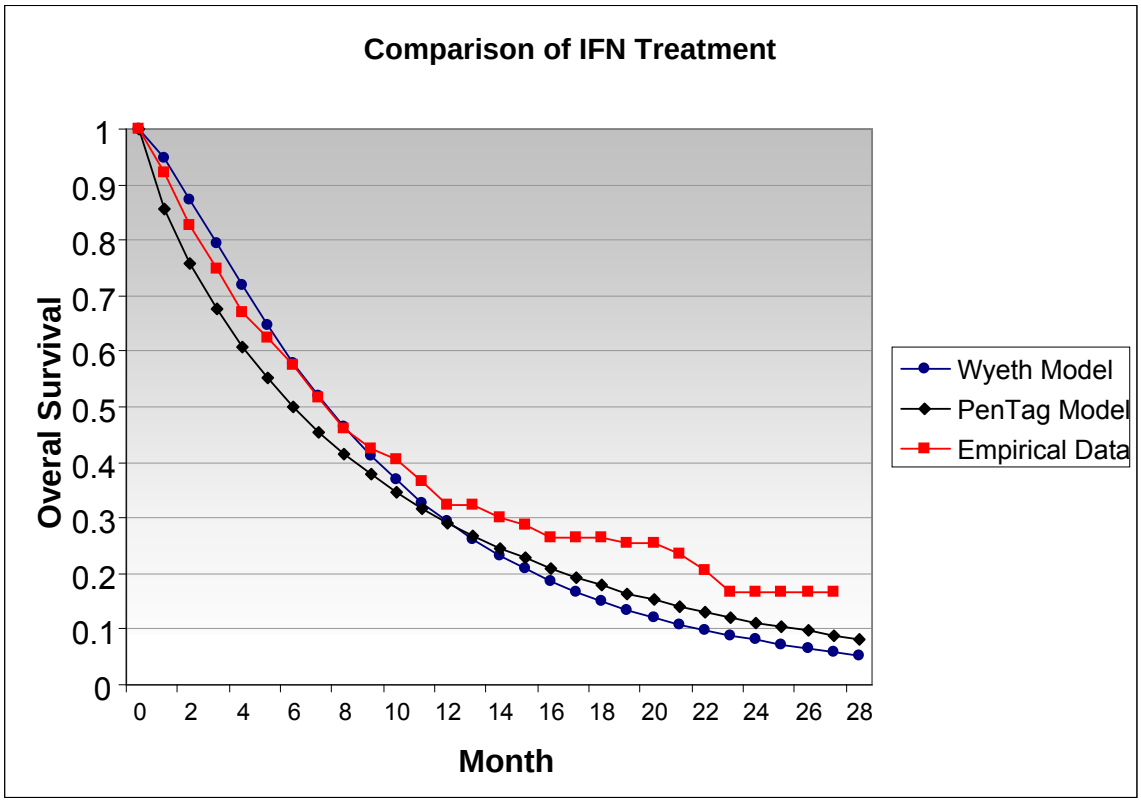


Figure 3. Comparison of overall survival, Interferon



Comparison of Statistical Methods in Weibull Function Estimation

In addition to the use of the different progression assessments, the PenTAG and Wyeth models use different methods in estimating the Weibull function parameters. PenTAG used secondary data exacted from the Hudes et al. study, and estimated the Weibull functions of IFN treatment by using a simple linear regression after transforming the Weibull survival function into a linear function. The PenTAG group then assumed the temsirolimus treatment group has the same Weibull shape and scale as the IFN treatment group and apply the hazard ratio obtained from the Hudes et al paper to the IFN survival curve to estimate the PFS and OS of the temsirolimus group. Statistically, this method is a "second-best choice", and is used when there is no patient-level trial data available. One of the major disadvantages of this method is that it may have a poor fit for the second group estimated by the application of the hazard ratio (i.e., temsirolimus), although it may provide a good fit for the first treatment group. In their report, the PenTAG group failed to provide their fit on temsirolimus treatment. Another disadvantage of this method, as mentioned in p.255 of the PenTAG report, "…at large time t, the number of patients in PFS is modelled to exceed the number of patients alive."

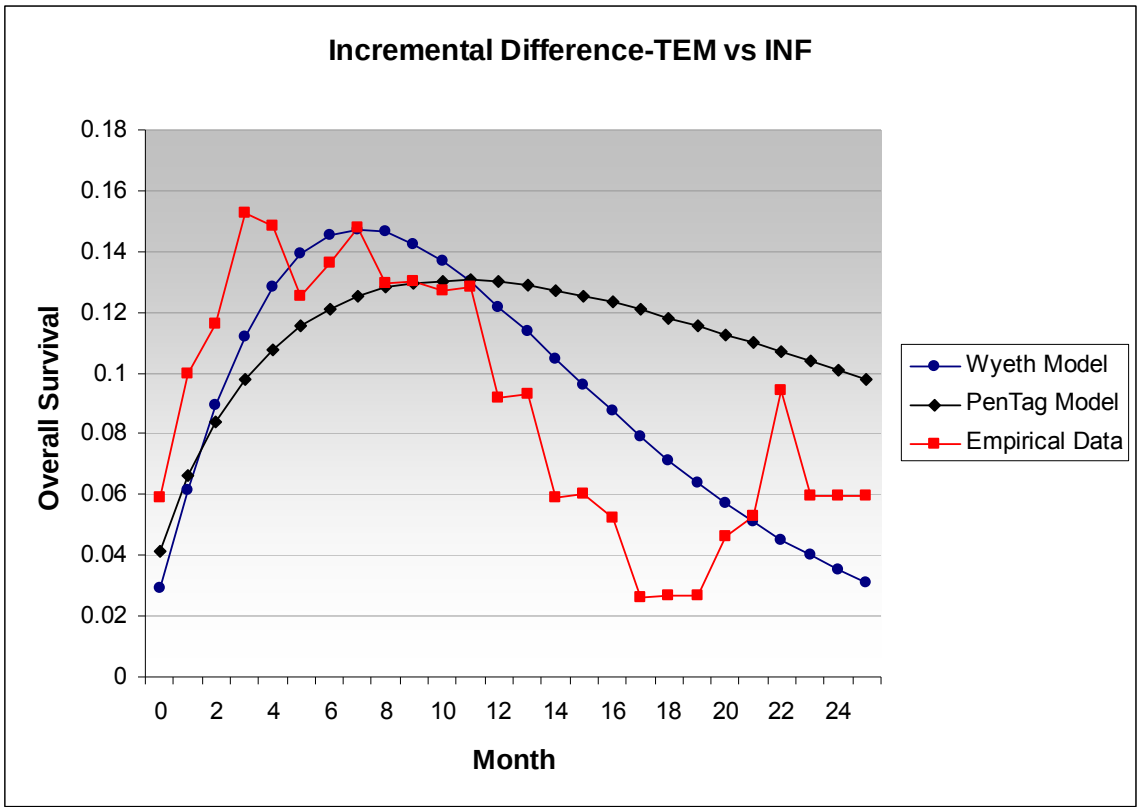
The Wyeth model used the patient-level data directly from the trial (the same trial data analyzed in the Hudes et al. paper) and conducted survival regression by using the following Weibull hazard function:

$$h(t) = \exp(x\beta) * (\gamma\lambda t^{\gamma-1})$$

Where x includes intercept and treatment variable TX (TX=0, TEM; TX=1, IFN), λ is the scale parameter and γ is the shape parameter. This approach avoided the problems caused by the PenTAG method, and gives a relatively good fit for both temsirolimus and IFN treatment groups. Another advantage of this approach is that a comprehensive and more accurate probabilistic sensitivity analysis can be performed by using Weibull covariance parameters and the Cholesky decomposition method.

Figure 4 below compares how these two fit methods performed in predicting the incremental difference in overall survival (undiscounted, OS in temsirolimus group – OS in IFN group).

Figure 4. Comparison of incremental survival between treatment groups by multiple fit methods.



The sections "Wyeth Derivation of Transition Probabilities" and "Comparison of Statistical Methods in Weibull Function Estimation" in this document contain comments that are also relevant to criteria S4, S8 and D2 in the critical appraisal checklist in Appendix 6 (pages 244-245) of the AR.:

In terms of criterion D2b, as described above, we estimated three Weibull functions and the hazard ratios can be derived from those Weibull functions. In the Weibull function we presented previously, a variable for treatment group is included and treatment effect IS estimated (though not in the form of a hazard ratio). The Weibull model parameterisation is provided in the table below. We did not calculate hazard ratios explicitly because the Weibull parameters were used directly to calculate the survival probabilities. Also, we did not calculate hazard ratios on PFS and OS because these would not be used in the model calculation.

Weibull Model Parameterization – Base case Model

Progression-free Survival 1 (transition due to death event)	**DF**	**Estimate**	**Standard Error**	**95% CI Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept	1	2.981	0.1157	2.7542	3.2077	664.11	<.0001
Interferon alpha	1	-0.6442	0.142	-0.9224	-0.3659	20.59	<.0001
Temsirolimus	0	0	0	0	0	.	.
Scale	1	0.8065	0.0508	0.7128	0.9126		
Weibull Shape	1	1.2399	0.0781	1.0958	1.4029		

Progression-free Survival 2 (transition due to progression event)	**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept	1	2.4121	0.0871	2.2414	2.5828	767.11	<.0001
Interferon alpha	1	-0.1215	0.1313	-0.3788	0.1358	0.86	0.3547
Temsirolimus	0	0	0	0	0	.	.
Scale	1	0.9417	0.051	0.8469	1.0472		
Weibull Shape	1	1.0619	0.0575	0.955	1.1807		

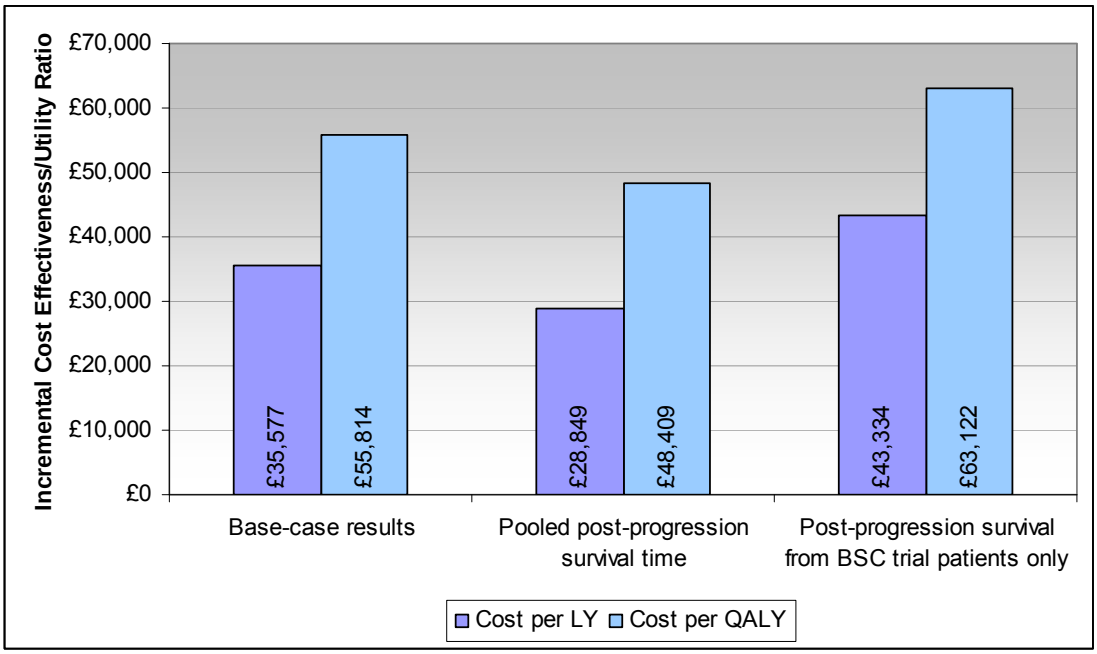
Survival – Post-progression	**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept	1	1.9822	0.163	2.2072	2.8463	240.17	<.0001
Interferon alpha	1	0.1813	0.255	-0.4076	0.5919	0.13	0.7178
Temsirolimus	0	0	0	0	0	.	.
Scale	1	1.0978	0.1044	0.6091	1.0227		
Weibull Shape	1	0.9109	0.1675	0.9778	1.6418		

Time of Treatment	**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept	1	1.8574	0.0686	1.723	1.9919	733.24	<.0001
interferon alpha	1	-0.4548	0.0964	-0.6438	-0.2659	22.26	<.0001
Temsirolimus	0	0	0	0	0	.	.
Scale	1	1.0304	0.0379	0.9587	1.1074		
Weibull Shape	1	2.235	0.2269	1.8318	2.727		

The most significant structural uncertainty (criterion D4b) was in the post-progression survival given the smaller sample size on which the Weibull estimates were based (versus during PFS). The results of an analysis conducted using pooled data from both the IFN alone and temsirolimus alone treatment arms, and a second analysis using only patients who received

no subsequent active treatment (this analysis again used treatment group as an independent variable in generating the Weibull parameter estimates) are presented in figure 5.

Figure 5. Effect of different post-progression survival estimates on model outcomes



Criterion C1 covers the internal consistency of the model. The calculation links and logical formulas were checked and validated by a peer reviewer. Face validity was assessed by comparing the median estimates of PFS and OS derived in the model base case analysis and those observed from the Phase III trial. One-way sensitivity analysis was conducted varying individual inputs to assess their impact on model results. In sensitivity analyses, the model behaved as expected.

C2: External consistency

The PFS and OS predicted by the Wyeth model were compared to the estimates from the empirical trial data only, given that external data that reflect a poor prognosis population are scarce. The estimated medians generated by the model analysis for PFS and OS were validated against the median OS results of the trial (for the independent progression estimates) as reported in the Clinical Study Report. As discussed in the responses above, the inputs derived for our model for PFS are based on different outcomes than those presented in the Hudes et al. paper (site investigators' assessment). The predicted OS generated by the Wyeth model does generate a good approximation of that presented by Hudes et al. over the first year, but does not fit as well for subsequent time.

Section 4.4.1.1

As mentioned previously, we surveyed 15 practising RCC Oncologists on the administration of IFN specifically in patients with 3 of 6 poor prognostic factors. Feedback from these Oncologists suggests that IFN treatment is generally limited to 1 year; patients on IFN visit hospital monthly, there may be more frequent visits at start of treatment and the visits may be less frequent if patient is tolerating IFN well. Conversely, patients experiencing toxicities will be seen more often.

The reported percentage of patients administering IFN at home ranged from 50-100% depending on the oncologist, and those administering at home were reported to have the support of a District nurse, a healthcare at home specialist nurse (Roche funded at present) or the patient's GP. Most centres had a support service available via telephone to Specialist nurse, outpatient department or Healthcare at Home.

The PenTAG model seems to have accounted for some but not all of these costs. In addition, patients in the Hudes study are in a worse health state than patients with good or intermediate risk prognosis as suggested by the utility scores. Moreover, IFN patients in the trial achieved only 56% of the target dose, which translates into many more cases of delay or reduction of IFN dose compared with the other economic models where the IFN dose intensity was above 83%. The poorer dose intensity involves more frequent decision making and, thus, more patient contacts with medical professionals for advice and possibly treatment of AEs. Again, these considerations have not been taken into account in the PenTAG model and 'for consistency' patients on IFN have been treated in the same way irrespective of their prognosis. As a result, the costs of patients on IFN in the temsirolimus economic model by PenTAG have been underestimated.

Section 4.5.4.5 table 39 page 146

Error in table. IFN 18MU referred to as 2nd line when it should be first line.

Section 4.5.4.5, page 147

Regarding the lack of administration costs attributed to the oral tyrosine kinase inhibitors, it should be noted that on the 22nd January 2008, a rapid response report was issued by the National Patient Safety Agency (http://www.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=7524). In the report it was stated that oral anti-cancer medicines, including sorafenib and sunitinib must be administered and monitored to the same standard as injected therapy. This was following reports of three recent deaths and a further four hundred patient safety incidents concerning oral anti-cancer medicines between November 2003 and July 007. Half of these reports concerned the wrong dosage, frequency, quantity or duration of oral anti-cancer medicines. They also stipulated that there are substantial numbers of unreported incidents.

The report states:

- Healthcare organisations should prepare local policies and procedures that describe the safe use of these oral medicines.
- Treatment should be initiated by a cancer specialist.
- All oral anti-cancer medicines should be prescribed only in the context of a written protocol and treatment plan.
- Non-specialists who prescribe or administer on-going oral anti-cancer medication should have ready access to appropriate written protocols and treatment plans including guidance on monitoring and treatment of toxicity.
- Staff dispensing oral anti-cancer medicines should be able to confirm that the prescribed dose is appropriate for the patient, and that the patient is aware of the required monitoring arrangements, by having access to information in the written protocol and treatment plan from the hospital where treatment is initiated and advice from a pharmacist with experience in cancer treatment in that hospital.
- Patients should be fully informed and receive verbal and up-to-date written information about their oral anticancer therapy from the initiating hospital. This information should include contact details for specialist advice, which can be shared with non-specialist practitioners. Written information, including details of the intended oral anti-cancer regimen, treatment plan and arrangements for monitoring, taken from the original protocol should be given to the patient. When shared with pharmacists and dispensing staff, this would enable the above dispensing requirements to be satisfied.
- Full use should also be made of NHS cancer centre web sites to provide information for healthcare staff, patients and carers to ensure the safe use of oral anti-cancer medicines.

Therefore the safe use of oral anti-cancer medicines implies there would be administration costs of the oral TKIs, that should be accounted for in the economic evaluation.

<u>Section 4.5.7.2. Research/Policy Question 3 - Cost effectiveness of temsirolimus compared to IFN as first line therapy</u>

The sub-group cost-effectiveness analysis in this section reports results for patients based on their nephrectomy status, type of RCC and Motzer (MSKCC) severity score. However, when compared with the results of the base case analysis, there appear to be some issues that should be addressed by PenTAG:

- The attempt to isolate a subgroup of patients that fit the MSKCC poor prognosis score is unnecessary as it is a deviation from the EU licence of temsirolimus. However, when comparing Table 47 with Table 48, the poor prognosis patients on temsirolimus in the Motzer group seem to be on treatment for longer (12 months) compared to patients in

the base case analysis (7.6 months). With a gain in life years of 1.25 vs. 1.52 respectively that is not logical and suggests there may be errors in the model.

- Similarly, when comparing tables 47 and 48, there would appear to be an error in the calculation of the ICERs for clear and non-clear cell RCC as both ICERs are above the base case ICER for all patients.

Summary and Conclusions

Wyeth maintain that the pivotal phase III study identified in the AR demonstrates that temsirolimus treatment results in significantly superior efficacy, in terms of OS, compared with IFN treatment in patients with advanced RCC and with at least 3 of 6 risk factors. The economic model submitted by Wyeth is robust and demonstrates that temsirolimus offers a cost effective treatment option for the small number of patients with poor prognosis advanced RCC.

Table of comments

Section No.	Section Title	Page Number	Comments
1.1	Background	1	Sutent described as 'novel' – although temsirolimus may have greater claim to this..
1.5	Discussion	9	Blanket statement states 'large amount of uncertainty in estimates of overall survival', however temsirolimus has proven OS benefit
2.7.1.1	Pharmacology	27	The SmPC for Roferon-A (IFN) indicates that it should be administered under the supervision of a qualified physician experienced in the management of the respective indication. Appropriate management of the therapy and its complications is possible only when adequate diagnostic and treatment facilities are readily available. The assumption that 100% of patients can self administer IFN at home is therefore an overestimation and the associated costs of such administration in the PenTAG model (Table 40 p148) is underestimated.
2.7.4.3	Adverse events	30	AEs listed for temsirolimus are not correct. See text on p3 for detailed response.
2.7.4.4.	Cost	31	Cost of temsirolimus has been assumed to be £618 when Wyeth has provided a cost per vial of £515. All relevant results should be adjusted.
3.1.3.	Data extraction strategy	36	Second reviewer should be blind to the first reviewer's data extraction and not 'checking' it. See CRD Report 4 for details of the acceptable methodology.
3.1.4.	Quality assessment strategy	36	Same as above - the two reviewers should be independent
3.2.1	Quantity and quality of research available	42	Table 9 summarising published data and highlighting weaknesses/omissions. See CSR for detailed response.

3.2.4.1	Quantity, quality and characteristics of included studies	66	The additional criterion of "metastases in multiple organs" does reflect the poor nature of the prognosis of patients. The marketing authorisation describes directly the six prognostic risk factors that should be used to identify RCC patients eligible for treatment with temsirolimus. The assessment of temsirolimus should be carried out in the context of its EU marketing authorisation and hence there appears to be no need to attempt to re-define the patient group using a different set of risk factors/criteria, especially since, in the absence of data, no comparison with other relevant treatments within this appraisal has been possible.
3.2.4.1	Quantity, quality and characteristics of included studies	68	Stated 30% of patients in both groups would have been classified as having intermediate prognosis rather than poor prognosis. See comment on p3.
3.2.4.2	Assessment of clinical effectiveness	71	Although the CI may seem wide the p-value is indicative of the statistical significance of the hazard ratio. Moreover, temsirolimus is the only drug with a CI that does not cross unity and the phase III data have satisfied the Regulatory authorities in granting marketing authorisation. See comment on p3.
3.2.4.2	Assessment of clinical effectiveness	75	Errors in table – See text on p4 for detailed response.
3.2.4.2	Assessment of clinical effectiveness	76	AE data – See text on p3 for detailed response.
3.2.4.2	Assessment of clinical effectiveness	78	Subgroup analysis: errors in table 25 and 26. See text on p4 for details.
3.2.4.2	Assessment of clinical effectiveness	80	HR and CI in Table 27 do not match those in the abstract (both for prior and no prior nephrectomy). Correct values are cited on p4 of this document.
4.4.1.3	Temsirolimus (manufacturer analysis/model)	122	Cost of admin of IFN not adjusted by dose intensity: Patients with poor prognosis on IFN achieved only 56% of the targeted dose in the temsirolimus study, hence that would require decisions on whether to delay or reduce the next dose on many more occasions compared to the use of IFN in the studies of the other drugs included in this appraisal where the dose intensity was much higher (83% or above) in the PenTAG model.
4.4.1.3.	Temsirolimus (manufacturer analysis/model)	122	Cost of 2nd line drugs: there is an option in the model to include the cost of 2nd line drugs, however the model assumes 0% use of 2nd line drugs and 100% BSC. See also p. 39 in the Wyeth Submission.

4.4.1.3.	Temsirolimus (manufacturer analysis/model)	123	"The time horizon is short, at 3-years, but appears to capture the main impacts of disease and treatment, although it has not been tested in sensitivity analysis." Note that the model reports results at 12 and 24 months and not just at 3 years.
4.4.1.3	Temsirolimus (manufacturer analysis/model)	123	“It is important to remember the definition of poor prognosis used in the trial differs from MSKCC prognosis scale.” This definition of poor prognosis is used in the marketing authorisation where the prognostic risk factors are clearly specified. See also comments above referring to p.66.
4.4.1.3	Temsirolimus (manufacturer analysis/model)	123	Concerns over structure of model - please refer to item 3. in the text of this document for a detailed response.
4.4.1.3.	Temsirolimus (manufacturer analysis/model)	123	As noted above – there is an option in the model to include the cost of 2nd line drugs, however the model assumes 0% use of 2nd line drugs and 100% BSC. See p. 39 in the Wyeth Submission.
4.4.1.3.	Temsirolimus (manufacturer analysis/model)	124	Shape of survival curves - please refer to item 3. in the text of this document for a detailed response.
4.4.1.3.	Temsirolimus (manufacturer analysis/model)	126	IFN - 25% district nurse, and 75% self administered. See text on p12 for detailed response.
4.4.1.3	Temsirolimus (manufacturer analysis/model)	126	There is sufficient level of detail regarding the overfill of the vial and the availability of an overfill provides the opportunity for batching - see Wyeth submission p. 46. We have addressed this opportunity in the sensitivity analysis as we do appreciate that it may not be appropriate in all settings.
4.5.4.3	Effectiveness data	138	The attempt to isolate a subgroup of patients that fit the MSKCC poor prognosis score is unnecessary as it is a deviation from the EU licence of temsirolimus and is based on further assumptions that introduce further uncertainty in the analysis. Furthermore Table 48 erroneously suggests that time on treatment in the Motzer poor prognosis patients is longer than for the overall group. See text on p3 for detailed response.
4.5.4.3	Effectiveness data	139	Appear to have misquoted subgroup clinical effectiveness data. See text on p14 for details.
4.5.4.5	Resource Use / Cost data inputs	144	Incorrect price in Table 38 - requires re-run of the model and all relevant sensitivity analyses.

4.5.4.5	Resource Use / Cost data inputs	146	Table 39 refers to IFN as 2nd line rather than 1st line in poor prognosis patients.
4.5.4.5	Resource Use / Cost data inputs	147	Regarding the lack of administration costs attributed to the oral tyrosine kinase inhibitors, the rapid response report issued by the National Patient Safety Agency (NPSA) implies that for the safe use of oral anti-cancer medicines there would be administration costs of the oral TKIs, that should be accounted for in the economic evaluation.
4.5.4.5	Resource Use / Cost data inputs	147	The cost in Figure 15 should be re-calculated in view of the correct vial price for temsirolimus
4.5.4.5	Resource Use / Cost data inputs	151	Cost associated with adverse events state they do not expect to see any differential resource use: in comparison with temsirolimus that is **not** due to a similar AE profile/costs but rather due to the shorter duration of IFN treatment.
4.5.7.2	Research/Policy Question 3 - Cost effectiveness of temsirolimus compared to IFN as first line therapy	165	The PenTAG model was compared with the results of the Wyeth submission, however, the AR does not provide the Wyeth main results table for comparison - see Table 7, Appendix A in the Wyeth submission.
4.5.7.2	Research/Policy Question 3 - Cost effectiveness of temsirolimus compared to IFN as first line therapy	169	Table 48: Subgroup analyses: Clear and non-clear cell sub-groups of patients both have ICERs that are greater than the ICER for all patients - that is not expected and sugests errors in the model. There are inconsistencies in the reported costs and benefits for the sub-group defined as Motzer poor prognosis patients. See text on p15 for details.